8. The importance of the drug platform: coated, uncoated, sleeves, and new concepts

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BACKGROUND

Restenosis has been the most important limitation of percutaneous transluminal coronary angioplasty (PTCA). For almost two decades therapeutic approaches to restenosis focused on the delivery of agents to the vessel wall by systemic or intracoronary methods. Despite the large number of therapeutic compounds evaluated in preclinical studies, little impact on clinical outcomes was realized in part due to inadequate local drug concentrations in the coronary vessel wall. Direct intracoronary infusions and the application of intracoronary delivery catheters to infuse agents either luminally or murally into the coronary artery have had limited success due to short drug–vessel wall interaction time, rapid drug washout, and vessel wall injury due to high pressure transfer.

Siegel first proposed the use of stents as delivery platforms for vascular drug delivery [1]. Lambert et al. presented comprehensive kinetic studies, which demonstrated that forskolin, a nonpolar adenosine cyclase activator, could be delivered via polymer-coated stent to the arterial wall and that concentrations several orders of magnitude greater than that in blood or other remote organs could be achieved. Further, a first-order kinetic release was demonstrated [2]. Sustained local delivery of agents directly to the coronary would appear to be an attractive approach to address restenosis because it avoids many of the limitations of systemic therapy. This chapter focuses on some of the practical and theoretical considerations related to new concepts in vascular drug delivery.

THEORETICAL CONSIDERATIONS

There is as yet no perfect drug delivery platform. In fact, the ideal parameters for any drug delivery system would be dictated by the specific clinical considerations. The physiochemical properties of the drug are critical. Lipophilic compounds such as paclitaxel tend to partition in the vascular wall, which then acts as a drug reservoir for some period of time [3]. As such, a release kinetic that is relatively rapid may be acceptable for such drugs though what is "rapid" for this drug as opposed to what is "prolonged" is biologically unknown at this time. Highly water-soluble compounds such as heparin will be rapidly mobilized from the vascular wall and residence times will be briefer than compounds with greater lipophilicty. A rapid first-order release kinetic would be acceptable if the intended duration of the drug's action is brief, for example, local anti-thrombotic effects. If more prolonged local action were required, for example, restenosis prevention, then a delivery system capable of sustained release would be required.

A second consideration for a local vascular release system would be the delivery to achieve high mural drug concentrations without systemic or local toxicity or inflammation. In most, but not all systems, the drug is "carried" on a polymer delivery system and then released by some mechanism at the site of local delivery. One notable exception currently being utilized is the Cook Inc., paclitaxel product. In this device, the drug is bound to the stent.

Polymer delivery systems can broadly be categorized as either bio-stable or bio-erodable, though a variety of nomenclatures are used.

The former type polymers are currently in use in the Johnson and Johnson sirolimus product as well as the Boston Scientific paclitaxel product. In this scenario the drug is released, usually by first-order kinetics by the process of diffusion. A variable amount of drug may be retained in the polymer for long periods of time. As of this writing, available clinical data would support the short and intermediate term safety of these particular polymers though there will be need to observe patients for longer periods of time to assure that there is no delayed toxicity from latent polymer degradation or drug effect.

Bio-erodable polymers release drug as they erode or decay. They can be broadly thought of as "bulk eroders" or "surface eroders." Bulk eroders are ananologous to ice cubes and release drug as the mass of polymers shrinks. Surface eroders release drug as the surface is dissolved. Examples of bio-erodable compounds include polylactic acid (PLA) and polylactic glycolic acid (PLGA). These compounds are quite heterogeneous and vary by monomer composition and molecular weight. These parameters influence many properties including water solubility, release rates, and tissue inflammation. The potential limitation of these compounds can be their ability to break apart as they erode and the consequent release of particulates. They also may reduce the pH of the local microenvironment. This not withstanding, they may be used effectively and safely if attention is taken with molecular weight and coating methodology so that inflammation and particulate may be avoided [4,5].

In the case of drug delivery stents, uniformity of drug delivery is desirable. Manufacturers will attempt to uniformly and homogeneously apply the drug and/or polymer. Failure to achieve such uniformity would result in variable dose distribution to the vessel wall. This could yield "hot" or "cold" spots, which may affect drug efficacy, toxicity, or safety. This becomes especially important during stent expansion where polymer cracking or thinning may occur. Further, such cracking of the polymer may result in release of particulates. In the case of self-expanding stents or other designs that are delivered with a coating or a sheath, consideration should be given to the physical stability of the system with respect to drug and polymer retention following the interaction of the sheathing system with the polymer and drug.

PRACTICAL CONSIDERATIONS

Coated platforms. The Johnson and Johnson "Cypher" drug-eluting platform utilizes 10 μg thick layer of a 50 : 50 non-erodable methacrylate and ethylene-based copolymer, and 30% sirolimus by weight applied to the surface of the Cordis Bx velocity stent [6]. The addition of a drug-free polymer matrix (topcoat) to introduce a diffusion gradient prolongs drug release to >28 days in the slow release formulation. Preclinical studies showed a 750 μg polymer coating is biocompatible at 60 days in both the porcine and canine models [7]. The RAVEL (randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization) study randomized patients to a sirolimus-eluting stent (140 μg sirolimus/cm^2 of metal surface area) or to an uncoated Bx velocity stent. Total sirolimus content was 153 μg on the 6-cell stent (2.5 and 3 mm) and 183 μg on the 7-cell stent (3.5 mm in diameter). Impressive results at 6 months showed 0% late loss, 0% binary restenosis, 0% target lesion revascularization (TLR), and only 5.8% major adverse cardiac events (MACE) in the sirolimus group [8]. In the SIRIUS (sirolimus-eluting stent in de novo native coronary arteries) trial, there was a 3.2% restenosis (in-stent) compared to 35.4% in controls, and 8.9% in-segment restenosis rate compared to 36% in controls. Nine-month MACE was 8.6% versus 21% in control, primarily due to a reduction in TLR.

Restenosis in the sirolimus group was predominately seen at the proximal peri-stent margin. The authors concluded that limiting the area of balloon injury to match the stented zone, the use of longer stents to cover reference vessel disease, the avoidance of gaps between stents, and intravascular ultrasound (IVUS) guided stent deployment to ensure full stent apposition, should be technique modifications that operators should make in deploying these drug platforms [9]. This data, though exciting and very impressive, leaves further questions and room for improvement. What is the mechanism of the reduced efficacy seen at the proximal stent edges? Was it merely failure to stent "from good to good" as some have speculated or are there more complex factors related to drug release, migration, or effect? One possibility is that the lipophilic sirolimus molecule partitions such that injury from the proximal end of the stent and balloon is not properly "covered." Then why is the effect seen only at the proximal end of the stent when vessel tapering should if anything increase injury at the distal end? Could there be luminal drug effect on the distal segment? The answers to these intriguing questions must await further experimental and clinical studies.

Careful analysis of the available SIRIUS data would appear to indicate that the benefit of the sirolimus stent is attenuated in smaller vessels. In the subset of patients with vessel diameter of 2.5 mm, dichotomous restenosis rates in the range of 15% were seen. It appears therefore that the ability to completely reduce intimal hyperplasia in this setting is suboptimal. The challenge will be to titrate drug effect such that "pathologic" hyperplasia is eliminated but yet to allow for sufficient healing and intimal regrowth to safely incorporate the stent into the arterial wall.

The Boston Scientific TAXUS (TAXOL USA) drug-eluting program has centered around the delivery of paclitaxel using a non-erodable polymer surface coating on initially the NIR Conformer stent (TAXUS I–III), and latterly on the Express II stent (TAXUS IV). The non-erodable poly(lactide-co-caprolactone) copolymer (pLA/pCL) has been shown to have similar inflammatory properties, restenosis, and endothelial coverage to uncoated bare metal stent out to 56 days in the rabbit model [10]. The TAXUS I pilot study showed no binary restenosis at 6 months in the slow release 1.0 $\mu g/mm^2$ paclitaxel on the NIR conformer compared to 10.3% for the uncoated NIR stent. Six-month MACE was 0% versus 6.7% in control. In Taxus II (Columbo A. Transcatheter Therapeutics, Washington DC, September 2002), the total dose was similar, however two different paclitaxel release patterns were studied. In the slow release arm, 6-month binary restenosis was 2.3% versus 17.9% for control ($p < 0.002$) with MACE of 8.5% versus 19.5%, $p = 0.013$. Similar findings were seen in the moderate release group versus control. The moderate release arm had a biphasic release of paclitaxel with early burst release in the first 48-hours followed by a slower 10-day lower level phase. There was no evidence of edge effect in either study. Of interest, at the recent FDA advisory panel meeting (November 2003), it was discussed that the longer release rates seemed to be associated with less evidence of drug toxicity in the porcine models.

This BiodivYsio/Abbott drug delivery platform uses phosphorylcholine (PC) attached to the surface of a BiodivYsio stainless steel stent via a methacrylate polymer basecoat. This basecoat can serve as a reservoir for drug loading. The PC polymer is an inert and stable coating that via a sponge-like mechanism can absorb a drug into the polymer, subsequently to be eluted into the desired vessel over a prolonged period of time. The polymer has a smooth coating that is only 1 μ thick and is thromboresistant. The PC coating has been shown to endothelialize normally and does not produce any adverse tissue reaction in animal models [11]. In addition, PC-coated stents have

been shown to have equivalent restenosis rates versus bare metal stents in clinical studies [12]. The STRIDE registry, which eluted dexamthasone from the BiodivYsio platform, showed a 13% binary restenosis rate. The BRILLANT trial using the matrix metalloproteinase inhibitor, Batimastat, did not show benefit. Abbott intends to elute the rapamycin analogue, (ABT-578) using this drug platform. A pilot clinical trial is now underway.

For the Guidant Actinomycin-D drug-eluting program, the drug-platform utilized a non-erodable copolymer of ethylene and hydrolyzed vinyl acetate coated to the Mulitlink Tetra-D stent. Controlled release of the drug was achieved by the use of three polymer layers: a 5–6 μ polymer matrix top layer, a thinner actinomycin-D/polymer matrix middle layer, and a polymer matrix primer layer attached to the stent surface. Animal studies for a dose of 40 $\mu g/cm^2$ actinomycin-D show that 32% is released within 24 hours and 90% released by 28 days. Polymer properties do not delaminate with sterilization or deployment, and a low risk of hydrolytic or oxidative chain scission. The phase I ACTION (actinomycin improves outcomes by inhibiting neointimal hyperplasia) study randomized patients to three arms: a high dose actinomycin-D arm (10 $\mu g/cm^2$ of metal surface area); a low dose (5 $\mu g/cm^2$ of metal surface area); and the bare metal Multilink Tetra stent. MACE at 30 days showed three non-Q wave MI in 2.5 $\mu g/cm^2$ group, one non-Q wave MI in 10 $\mu g/cm^2$ group, and none in control group. Review of clinical data at 3 months showed high TLR rates related to clinical events including one late death and one late Q wave MI, resulting in termination of the trial. This trial was considered a failure. Some speculation exists as to whether this failure was drug or polymer related—or both.

The Biosensor drug-eluting stent program utilizes a 4–10 μ thick bio-erodable PLA polymer which is coated to the surface of the Biosensor Challenge stent. The PLA used is slowly degrading and appears to be fully biocompatible in preclinical studies [5]. Everolimus is eluted by rapid resorption of an amorphous glassine solid, which is a 50 : 50 combination of everolimus and PLA polymer. Results from the FUTURE I (first use to underscore reduction in restenosis with everolimus) were recently presented and appear to provide late loss and restenosis rates similar to that seen with the Cypher product.

Uncoated platform. The first drug-coated stent was the Cordis heparin-coated Palmaz-Schatz stent. Heparin is bound to the stent surface by the Carmeda method where heparin is immobilized to the stent by endpoint fragments that are covalently bound to polyamine-dextran adsorbed to the stent. In the BENESTENT-II pilot trial, there was zero subacute thrombosis in patients who received the heparin-coated Palmaz-Schatz stent. Recently, the Cordis HEPACOAT heparin-coated Bx velocity stent has been released. However, in the current era of excellent parenteral and oral antiplatelet therapy, additional benefit of the heparin-coated stent remains unclear.

Paclitaxel is another drug which can be applied to the stent surface without a polymer coating. To ensure uniform drug distribution, a stent with uniform stent strut spacing and low recoil is required. The drug needs to be attached to the stent in a way that there is no large loss of drug during stent expansion. This completely abolishes the possibility of a polymer-induced inflammatory response, however large amount of drug may remain on the stent indefinitely. Dip-coating metallic stents with paclitaxel dissolved in a solvent that is then evaporated off leaving a fine residue of paclitaxel adherent to the stent, was performed in the porcine model. Reduction in neointimal thickness was seen with the high dose versus bare metal control [13]. However, there was a significant loss of the applied paclitaxel before it reached the tissues. The Cook drug-eluting program uses an uncoated drug platform where paclitaxel is applied directly to the

surface of the stent without the use of a polymer using a modified stent surface proprietary method. The ASPECT (Asian paclitaxel-eluting stent clinical trial) compared three doses: 0, 1.28, and 3.1 μg paclitaxel/mm^2, and showed a binary restenosis of 27%, 14%, and 4% respectively at 6 months ($p < 0.001$). Similar findings were seen in the ELUTES (evaluation of paclitaxel-eluting stent) Trial where 0, 0.2, 0.7, 1.4, 2.7 μg paclitaxel/mm^2 showed a dose-dependent response for binary restenosis with 20.6% for bare metal stent versus 3.1% for high dose ($p = 0.055$). Both the ASPECT and ELUTES trials showed dose-related inhibition of neointimal hyperplasia of a non polymer-based paclitaxel-eluting stent in patients with de novo lesions but both failed to show a reduction in MACE at 6 months.

The DELIVER trial utilized the Cook technology of non polymer-based coating of 3.0 μg/mm^2 paclitaxel on the Guidant Multilink Penta Stent. This trial utilizes the same dose of paclitaxel used in ASPECT and ELUTES trials. The results were announced in January 2003. This trial failed to show a statistically significant reduction in the endpoint though there was a positive trend. The 9-month TVF and in-segment restenosis rates in the treatment arm were 11–12% and 16–17% respectively, corresponding rates in the control arm were 14–15% and 21–22% respectively. The reason for this disappointing result is unknown. These authors believe that the findings are related to the too rapid a release of drug as compared to the Taxus system though others believe that insufficient drug amount was delivered.

The JOMED drug-eluting program has a nano-porous ceramic layer of aluminum oxide 300 nm thick (AlCove Surfaces, Essen, Germany) attached to the surface of a Flexmaster Jomed stent. This ceramic layer allows no heavy metal ion dissolution, good tissue biocompatibility, and high mechanical stability. The nano-cavities enable high dose loading and controlled drug release, and avoids the need for polymer coating. The PRESENT study compared the Flexmaster Jomed stent with the nano-porous ceramic layer versus the same stent with a low dose of tacrolimus. Although 30-day MACE was 0% in both groups showing safety, there was no benefit with the low-dose tacrolimus in reducing restenosis, suggesting a lack of potency. A high-dose tacrolimus group has been added to the trial. JOMED also have a PTFE stent graft that contains tacrolimus bound to a chondroitin sulfate and gelatin (CSG) film attached surface of its coronary stent graft for the treatment of saphenous vein grafts.

Sleeves. The QuaDDS-QP2 stent (Boston Scientific Inc.) is a slotted-tube, 316L stainless steel, balloon-expandable stent with multiple polymer sleeves that slowly release 7-hexanolytaxol (QP2, a taxane analogue). The drug is loaded into the biocompatible polyacrylate sleeve at 800 μg of QP2 per 2.4 mm of sleeve. The number of sleeves can vary with the size of the stent, with a maximum number of 5 sleeves on the 21 mm stent [14]. The SCORE (study to compare restenosis between QueST and QuaDDS-QP2) trial was the first large randomized trial comparing a drug-eluting stent to an uncoated bare metal stent, with the primary endpoint of target vessel revascularization (TVR). The study however was stopped prematurely due to a 9.4% incidence of stent thrombosis in the drug-eluting stent arm including four that occurred 6 months or after. There was also an increased incidence of periprocedural myocardial infarctions, thought to be related to side branch occlusion due to the polymer bands. These two factors lead to a 30-day MACE of 10.2%. The dose of the paclitaxel analogue used in this study was high, and IVUS showed that in parts of the stent there was an absence of neointimal covering of the stent struts, which may have a relation to the late thrombotic events [15]. For the treatment of in-stent restenosis, the encouraging results at 6 months was almost eliminated by 12 months, suggesting delayed neointimal growth. Several

factors have been postulated: high loss of drug loaded into the stents, and the presence of plastic sleeves covering 60% of the stent surface area resulting in a bulky stent with thick struts, resulting in a foreign body reaction that triggers inflammation and cell proliferation [16]. This product is an example of how a potentially efficacious drug can yield disastrous clinical results if delivered on an ill conceived and badly designed system. Fortunately other paclitaxel delivery systems have been more successful thereby salvaging paclitaxel as a potential agent for clinical use.

BIODEGRADABLE STENTS

Biodegradable stents present an intriguing alternative to conventional coated drug delivery stents. The concept would allow for sufficient mechanical support to "stent" the vessel but permit biodegradation or "disappearance" of the stent over time. Such a device could also act as a vehicle for delivering local therapy to the vessel wall. The Igaki-Tamai high molecular mass poly-L-lactic acid (PLLA) coil stent has been implanted in humans. The stent is initially self-expanded using heat transmitted by the delivery balloon, followed by further expansion using the delivery balloon. At 6 months, restenosis rates were 10.5% with TVR of 6.7%. IVUS showed that at 6 months the stent struts were still present. To effectively impact on tissue growth, the combination of anti-proliferative agents and the biodegradable stent may be necessary [17]. Other materials such as tyrosine-derived polycarbonates are also being evaluated as resorbable stent materials.

LIMITATIONS OF CURRENT DRUG-ELUTING STENTS

For the most part, these stent/drug platforms have utilized standard metallic stents coated with a thin (5–10 μ) elastomeric biostable polymer surrounding the struts yielding a low volume, small thickness, high surface area drug delivery system. Drug release rates approximate classic first-order kinetics where a fixed fraction of elutable drug is released per unit time as predicted by Fick's Law of diffusion [18]. Cumulative release curves show that a very large percentage of drug is released in the first 24 hours and in some cases, where the drug is attached directly to the stent surface, about one-third of the drug remains on the stent indefinitely. These release kinetics are difficult to substantially alter because they are governed by the physical chemical properties of drug and/or polymer and are proportional to surface area and inversely proportional to membrane thickness [19]. Early burst release can be somewhat retarded by adding a blank polymer topcoat at the expense of a thickening of the stent. The success and the toxicity of these stents may be related to the significant and rapid partitioning [20], of these lipophillic compounds in the adjacent vessel wall thus creating a second drug depot, rather than the drug platform itself.

Dehiscence or deformation of the surface polymer during expansion to large diameters could affect release of drug from the polymer or worse, embolize the polymer. Available coated stents have yet to load enough drug to allow potentially less toxic, nonpartitioning water-soluble drugs, and biologic macromolecules such as peptides, and oligonucleotides to be successfully delivered over a time course consistent with their mechanism of action. Possible late untoward effects with surface coatings include necrosis with aneurysm formation and stent malapposition to the wall. Late lumen enlargement was seen angiographically in 3% of patients who received sirolimus in the RAVEL trial [21]. In the IVUS substudy from the RAVEL trial, there was a 21% incidence of incomplete stent apposition in the sirolimus group compared to 4% in the uncoated stent group ($p < 0.05$). It may be that the anti-proliferative effect of retained drug may preclude growth of tissue between the

void between struts and vessel wall, or the antimetabolite effect of the retained drug may lead to necrosis and apoptosis, generating a new empty space between the struts and the vessel wall [22]. The incidence of stent malapposition was much lower in the US SIRIUS trial but still significantly higher than bare metal stent controls. Importantly, the incomplete stent apposition did not translate into late clinical events.

The wide scatter of restenosis rates seen in the bare metal control arms of the drug-eluting stent trial has refocused attention that underlying stent design has a strong effect on outcome and is important for developing an ideal drug platform. The Bx velocity stent has a binary restenosis rate of 36.3% for in-segment in the SIRIUS trial, compared to the 23.8% in-segment for the bare metal NIR stent in the TAXUS II study. Similarly, the ISAR STERO-2 (intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome) trial showed a 31.4% restenosis rate for the Bx velocity versus 18% for the original thin-strut Multilink stent [23]. The authors concluded that this was due to the thinner strut thickness of the Multilink stent. However, there were significant differences in stent geometry between the two stents and changing one parameter such as strut thickness results in changing other parameters so that the stent remains balloon expandable at reasonable pressures. Cobalt chromium alloy stents have a thinner stent strut thickness, but retain good radiopacity and radial strength. Multilink VISION stent system registry had a 6-month 16.9% binary restenosis rate and a 6.7% target vessel failure rate [24]. The metallic content of the stent strut also influences restenosis with gold-coated stents having increased restenosis over bare metal stainless steel stents [25].

NEW CONCEPTS

The idea of using drug-eluting stents to treat indications beyond restenosis is an exciting new concept. It may be possible to use specially designed drug platforms as a large reservoir for treating angiogenesis, acute myocardial infarction, sequelae of acute ischemia, remodeling, and vulnerable plaque. One such design is the Conor MedStent system (Figure 8.1A) which differs from conventional drug delivery stents in that the stresses and strains of stent expansion are concentrated in small, specially contoured features called "ductile hinges," which absorb all expansion forces. It is therefore possible to create holes or wells in the struts without sacrificing strength, scaffolding, or flexibility. The holes are filled with therapeutic drugs in a multilayered degradable polymer inlays, creating hundreds of individually adjustable drug reservoirs (Figure 8.1B). Within any given hole the stacking of inlaid polymer/drug can be varied to create a variety of

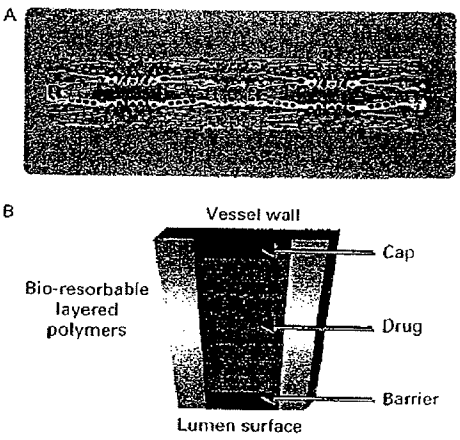

Figure 8.1

(A) The Conor MedStent™ metallic backbone; (B) cross-section of hole within strut containing multiple layers of biodegradable polymer. The cap layer reduces initial 24-hour burst release of drug. Layers degrade sequentially by erosion from vessel wall to lumen surface. The slower degrading barrier layer prevents loss of drug in to lumen.

controllable pharmacokinetic profiles. The use of slowly eroding barrier layers at the lumen surface allow preferential egress of drug in the direction of the vessel wall, with addition of cap polymer slowing the initial 24-hour burst release. In comparison to conventional stents with a 5–10 μ coating, the MedStent's polymer/drug volume is enlarged by 4- to 16-fold, polymer thickness is increased 14- to 28-fold, and polymer surface area is reduced by 64–81% These features permit expanded drug loading capacity and the ability to program the timing and spatial distribution patterns of drug release. Figure 8.2A shows the ability to deliver multiagent chemotherapy to the vessel wall with drug A released first followed by later delayed release of drug B. Multi-target chemotherapy can be programmed using this drug platform allowing release of one agent to the vessel wall to inhibit restenosis, with a second agent to be released to the lumen for treatment of diffuse disease or indications beyond restenosis (Figure 8.2B).

The bare stainless steel version of the Conor style stent was shown to be safe and effective in a 50-patient registry with P. Serruys as the Principal Investigator. There were no MACE at 30 days and the 6 month, angiographic in-stent restenosis rate was approximately 11.6% (personal communication from Principal Investigator).

The stent has been used in the Pisces trial evaluating different doses and release rates of Paclitaxil. This 180-patient trial which completed enrollment in December 2003 will be the first comprehensive evaluation of the role of variable kinetics, dose, and release direction on angiographic late loss. The Pisces kinetics/dose formulations are shown in Figure 8.3.

Recently, a Cobalt Chromium version of the Conor stent was developed. This stent, with a 0.037" crossing profile in the 3.0 mm version has the potential advantages of the Cobalt Chromium platform in a DES device (Figure 8.4). As of this writing, the Costar India trial, a replicate of the Pisces trial but with slightly different formulation kinetics is underway. The Eurostar trial, evaluating this device in multiple European centers is scheduled for early 2004.

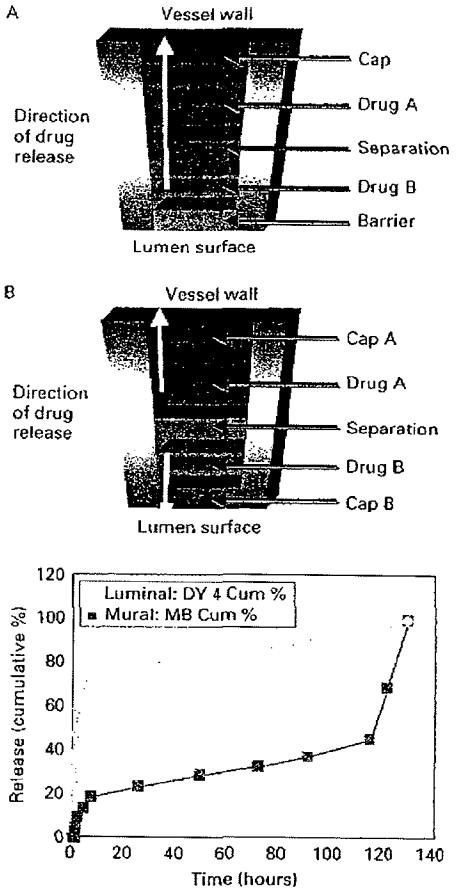

Figure 8.2

(A) This shows how multi-agent chemotherapy might be delivered to the peri-strut vascular wall with early release of "Drug A" and delayed release of "Drug B." (B) It shows a method to deliver multi-target chemotherapy with "Drug A" localized to the stented wall and "Drug B" eluted into the lumen for simultaneous treatment of vulnerable plaque or diffuse disease.

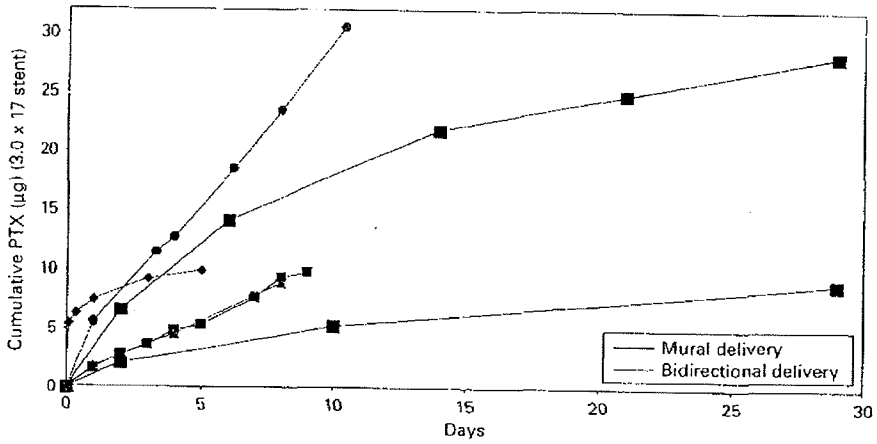

Figure 8.3

The Pisces trial is designed to determine the "optimal" formulation for Paclitaxil. Six variations are being evaluated and include very fast, moderate, and slower release, and 10 and 30 µg doses.

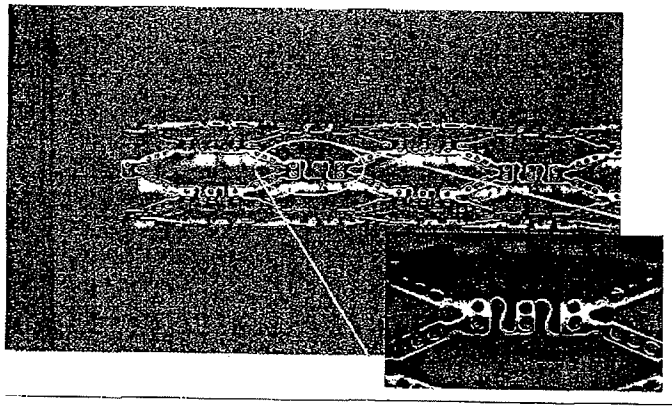

Figure 8.4

The Conor Cobalt Chromium platform has thin struts and low profile with the drug delivery reservoirs.

SUMMARY

In summary, some 15 years after they were first proposed, drug-eluting stents have emerged as the most significant therapeutic advance in Interventional Cardiology since the inception of the stent. Notwithstanding a variety of limitations, the era of angioplasty without the Achilles heel of restenosis is now beginning. In the future a variety of agents will likely be applied via an array of delivery

systems. Though restenosis is the first indication for vascular drug delivery we believe that other manifestations of atherosclerotic and ischemic heart disease will ultimately be addressed by luminal as well as mural delivery of therapeutic compounds.

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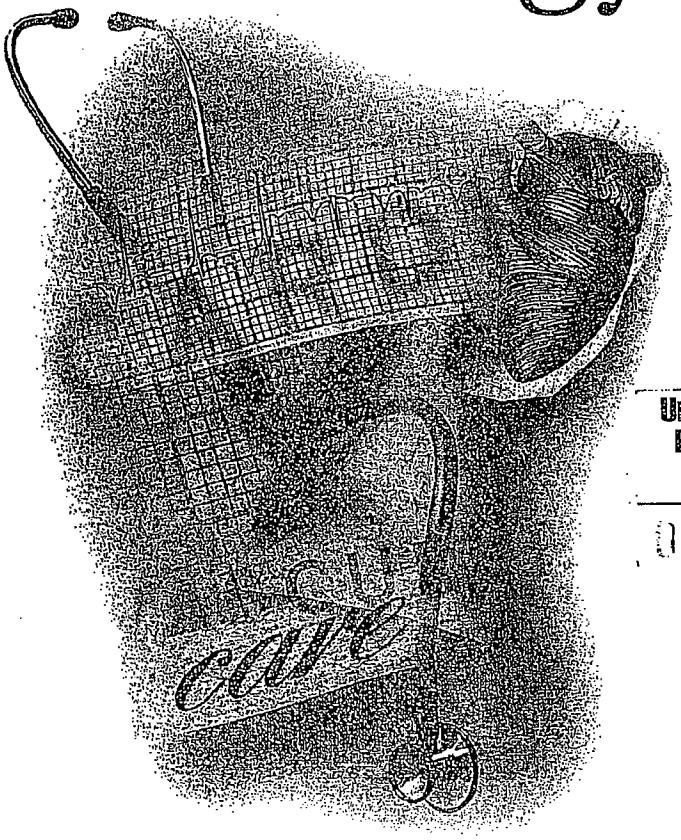

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(ISR) lesions, but there have been no comparative studies. Therefore, we compared 250 diffuse ISR lesions in 182 patients treated with ELCA (n = 124) or RA (n = 126). Baseline patient characteristics, total occlusions (8%), stent use (27%), and angiographic success (100%) were similar in the two groups.

Conclusions: (1) similar procedural results are achieved with both athero-ablative techniques; (2) there is a trend towards reduced in-hospital MACE with RA (? due to fewer SVG lesions); (3) despite smaller vessel size, RA has lower TLR, suggesting that higher ablation efficiency may impact late clinical outcomes. A randomized clinical trial comparing these different athero-ablative strategies for diffuse in-stent restenosis is indicated.

1129-92 Excimer Laser Coronary Angioplasty in In-Stent Restenosis: Acute and Long-Term Clinical Outcomes

Robert Slegel, Ambika Bhaskaran, Paul Underwood, Warren Breisblatt, Barbara Barker, Alvin Nuttall, Debbie Swanson, Peter Santos, Jennifer Vermillion. *Advanced Cardiac Specialists, Phoenix, Arizona, USA*

In-stent restenosis (ISR) is a serious limitation of coronary stenting (ST). Debulking procedures have been advocated in ISR to reduce in-stent neointimal tissue, improve final luminal diameter, and decrease the incidence of subsequent recurrence. We report our experience in the use of excimer laser coronary angioplasty (ELCA) for the treatment of ISR. From 1/98 to 8/98, ELCA was performed in 16 patients (mean age 63 years) presenting with angiographic evidence of ISR (>50% diameter reduction). Mean time following initial stent implantation was 4.1 months. Stents included Palmaz-Schatz (62.5%); GRII (25%); and AVE Microstent (12.5%). Of these, 31% presented with acute MI, while 56% presented with unstable angina. Target vessel distribution included: LAD (37.5%); RCA (56.3%); LMCA: 1. Lesions were ostial/proximal in 9 (56.3%); 2 lesions (12.5%) were in vein grafts. Ten stents had diffuse, proliferative restenosis while 6 stents showed intrastent focal lesions. Multiple passes were made with eccentric catheters to enhance the debulking procedure. Post-ELCA balloon dilatation was performed in all cases, with mean inflation pressure of 17.3 atm.

Results: Successful laser crossing and debulking (residual < 40%) was achieved in all cases, with post-balloon residual stenosis ≤ 20% and TIMI 3 flow. There was 1 major dissection post-ELCA, treated with prolonged balloon inflation. There were no major in-hospital events. At 12-month follow-up, 19% had clinical recurrence, requiring re-PTCA. There was no incidence of CABG or death. Event-free survival was 81%.

Conclusions: 1) ELCA with adjunctive balloon angioplasty appears to be safe and effective in the management of ISR. 2) Acute success is excellent. 3) At 1-year follow-up, TLR rates are acceptable with no death reported in this series. 4) Our initial experience indicates that debulking neointimal tissue by ELCA, with adjunctive balloon angioplasty, appears to be a promising treatment modality in in-stent restenosis.

1129-93 In-Stent Restenosis: "The Great Equalizer" – Disappointing Clinical Outcomes With ALL Interventional Strategies

Roxana Mehran, George Dangas, Gary S. Mintz, Ron Waksman, Mun K. Hong, Alexandre Abizaid, Andrea S. Abizaid, Ran Kornowski, Alexandra J. Lansky, John R. Laird, Jr., Kenneth M. Kent, Augusto D. Pichard, Lowell F. Satler, Gregg W. Stone, Martin B. Leon. *Washington Hospital Center, Washington, DC, USA*

In-stent restenosis (ISR) is due to neointimal hyperplasia and has increased in frequency with expanded stent use in complex lesions. This report summarizes the acute and long-term results of all interventional therapies (excluding brachytherapy) used for ISR in 821 consecutive lesions at the Washington Hospital Center. Baseline demographics were similar among the groups. ELCA, RA, and Stent were followed by PTCA in all cases.

	Overall n = 821	PTCA n = 314	ELCA n = 250	RA n = 126	Stent n = 131
Diabetes (%)	39.3	40.5	39.5	41.1	33.0
LL (mm)	13 ± 5	11 ± 2	16 ± 3	19 ± 3	†8 ± 2
Final %DS	19 ± 4	21 ± 2	17 ± 4	22 ± 3	†10 ± 1
Final CSA (mm^2)	7.3 ± 3.2	6.6 ± 0.8	6.9 ± 1	6.4 ± 0.5	†9.7 ± 1
1-year TLR (%)	27.9	26.6	31.6	23.1	27.0

†p ANOVA < 0.05, PTCA = balloon, ELCA = excimer laser, RA = rotational atherectomy, CSA = lumen area by intravascular ultrasound, DS = diameter stenosis, LL = lesion length, TLR = target lesion revascularization.

Using multivariate logistic regression analysis, independent predictors for TLR were: diabetes (OR: 1.63, p = 0.037), prior ISR (OR: 1.51, p = 0.041), and diffuse (LL > 20 mm) ISR (OR: 2.5, p = 0.001). Device choice was not a predictor of TLR.

Conclusions: Despite differences in interventional strategies, mechanisms of lumen enlargement, and final angiographic results, late clinical outcomes after treatment of ISR remain disappointing, and surprisingly independent of device choice. Thus, a definitive "cure" for ISR will require additional adjunct antiproliferative therapy, such as radiation vascular therapy which is under investigation.

1129-94 Angiographic Patterns of In-Stent Restenosis Lesions that Failed Radiation Therapy

Ron Waksman, R. Larry White, Rosanna C. Chan, Balram Bhargava, Gary S. Mintz, Lisa M. Gierlach, Alexandra Lansky, Lowell F. Satler, Roxana Mehran, Kenneth M. Kent, Martin B. Leon. *Washington Hospital Center, Washington DC, USA*

In WRIST-the Washington Radiation for In-Stent restenosis Trials – patients were randomized to placebo versus gamma radiation following PTCA. Twelve patients (7 native coronaries and 5 vein grafts) returned with recurrent angina and angiographic evidence >50% stenosis despite radiation therapy. The purpose of this analysis was to characterize the angiographic and intravascular ultrasound (IVUS) patterns of lesions with recurrent stenosis despite radiation. The angiographic patterns of recurrent stenosis were: focal stenosis n = 2, diffuse pattern (≥10 mm in length) n = 1, total occlusion n = 4, and edge stenosis n = 5. In 5 patients with edge stenosis the radiation ribbon/lesion length ratio was 1.05 suggesting inadequate coverage of the treated area by the radiation ribbon. Dosimetry analysis of the last seed in the ribbon (3 mm) detected 25% decrease in the dose compared to a seed located in the center of the ribbon. The 4 patients who presented with total occlusion were treated with a 13 seed ribbon (51 mm in length) and the ribbon/lesion length ratio was 1.54. IVUS analysis indicated increased lumen loss in larger stents and in larger vessel sizes with exaggerated tissue proliferation at the site of recurrence. The failed patients were treated with CABG n = 4, medical therapy n = 3 and repeat angioplasty n = 5.

Conclusions: The predominant patterns of radiation failures are edge stenosis and total occlusions. Special attention should be taken to position the source with wide treatment margins and to consider prolonged antiplatelet therapy when longer lesions are treated.

POSTER

1130 Peripheral and Carotid Interventions II

Tuesday, March 9, 1999, 9:00 a.m.–11:00 a.m.
Morial Convention Center, Hall F
Presentation Hour: 10:00 a.m.–11:00 a.m.

1130-38 Long-Term Follow-Up After Stenting for Iliac Stenoses and Occlusions

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Implantation of endovascular stents is a commonly used technique for percutaneous treatment of iliac stenoses. In contrast, the long-term efficiency of stents after recanalization of long iliac occlusions (LIO) remains uncertain. The objective of this study was to compare the results after stent-supported recanalization of iliac artery stenoses and occlusions.

In 246 patients a total number of 436 stents were implanted to stabilize suboptimal results after recanalization of high grade iliac stenoses (mean 84.7 ± 10.5%) (group A: n = 108) or total occlusions (group B: n = 138). The target lesion was localized in the common iliac artery (A: n = 56, B: n = 36), the external iliac artery (A: n = 33; B: n = 67) or both vessel segments (A: n = 19, B: n = 35). Length of the stented segment was significantly larger in group B (8.6 cm vs. 5.17 cm, p < 0.01).

Accordingly, more stents were needed after recanalization of LIO (1.99 vs. 1.49, p < 0.01). Comparing the clinical situation, we found a shorter walking capacity in group B as well as a reduced Ankle-Brachial-Index (ABI), measured after standarized treadmill test (0.57 ± 0.25 vs. 0.49 ± 0.15).

Results: A primary technical success (residual stenosis < 30%) could be achieved in 98.1% (group A) and 96.4% (group B) of patients, respectively. Clinically, a marked improvement of +2 or +3 grades according to the AHA-criteria was found in 62 pts. (57.4%, group A) and 117 pts. (84.8%, group B). During the mean follow-up of 19.5 months the primary patency rates were 87.0% in group A and 87.7% in group B (p = n.s). In the majority of cases reobstruction could be successfully treated by PTA, leading to secondary patency rates of 96.3% (group A) and 97.1% (group B).

In conclusion, endovascular stenting provides an effective treatment op-

Does the New Angiotensin Converting Enzyme Inhibitor Cilazapril Prevent Restenosis After Percutaneous Transluminal Coronary Angioplasty?

Results of the MERCATOR Study: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial

The Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group

Background. **Cilazapril is a novel angiotensin converting enzyme inhibitor with antiproliferative effects in the rat model after balloon injury.**

Methods and Results. **We conducted a randomized, double-blind placebo-controlled trial to assess the effect of cilazapril in angiographic restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA). Patients received cilazapril 2.5 mg in the evening after successful PTCA and 5 mg b.i.d. for 6 months or matched placebo. In addition, all patients received aspirin for 6 months. Coronary angiograms before PTCA, after PTCA, and at 6-month follow-up were quantitatively analyzed. In 94% of 735 recruited patients, PTCA was successful and all inclusion and exclusion criteria were met. For the per-protocol analysis, quantitative angiography after PTCA and at follow-up was available in 595 patients who complied with the treatment regimen (309 control, 286 cilazapril). The mean difference in minimal coronary lumen diameter between post-PTCA and follow-up angiogram (primary end point) was −0.29±0.49 mm in the control group and −0.27±0.51 mm in the cilazapril group. Clinical events during 6-month follow-up, analyzed on an intention-to-treat basis, were ranked according to the most serious clinical event ranging from death (control, two; cilazapril, three), nonfatal myocardial infarction (control, eight; cilazapril, 5), coronary revascularization (control, 51; cilazapril, 53), or recurrent angina requiring medical therapy (control, 67; cilazapril, 68) to none of the above (control, 224; cilazapril, 212). There were no significant differences in ranking.**

Conclusions. **Long-term angiotensin converting enzyme inhibition with cilazapril in a dose of 5 mg b.i.d. does not prevent restenosis and does not favorably influence the overall clinical outcome after PTCA.** (*Circulation* **1992;86:100–110)**

KEY WORDS • **clinical trials** • **cilazapril** • **angiotensin converting enzyme** • **percutaneous transluminal coronary angioplasty**

Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Andreas Gruentzig in 1977 as an alternative treatment for coronary artery bypass grafting (CABG) in patients with angina pectoris.[1] Increased experience and advances in technology have resulted in a high primary success rate (over 90%) and a low complication rate (death or nonfatal myocardial infarction, 4–5%).[2] However, the late restenosis rate (17–40%) still limits the long-term benefit of the procedure.[3–8]

From the Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group.

Supported by F. Hoffmann–La Roche Ltd., Basel, Switzerland.

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The cause of restenosis is unclear, but factors such as platelet aggregation, formation of mural thrombi, intimal proliferation of smooth muscle cells, elastic recoil, and active vasoconstriction at the site of PTCA injury have all been implicated.[9–17] A decade of intensive clinical and pharmacological research has not succeeded in altering the restenosis rate.[18,19] Various treatments started shortly before or after PTCA and sometimes given for up to 6 months, such as intravenous administration of heparin, antiplatelet therapy (aspirin, dipyridamole, ticlopidine, prostacyclin, ciprostene, thromboxane A_2 receptor blocker), anticoagulants (coumadin), calcium channel blockers (nifedipine, diltiazem, verapamil), and other agents such as corticosteroids and colchicine, have failed to reduce the restenosis rate.[20,21] Fish oil and cholesterol-lowering agents have shown promise, although the published results are conflicting.[20,22]

Balloon angioplasty extensively damages the medial smooth muscle cells as well as the endothelial lining of

the coronary vessel wall.[23] Recent data have shown that mitogens from platelets are not wholly responsible for initiating the proliferative response in balloon catheter–injured arteries, because smooth muscle cell proliferation occurred in the absence of platelets.[24] The smooth muscle cell proliferation was correlated with the severity of trauma inflicted by the denuding technique to the arterial wall, which would suggest a role for endogenous factors possibly released from damaged endothelial and smooth muscle cells.[12,25] The basic fibroblastic growth factor (bFGF) is one of the main factors, as it is released from disrupted cultured vascular cells and is a growth factor for smooth muscle cells in vitro and in vivo.[24,26] Platelet-derived growth factor (PDGF) may regulate the migration of smooth muscle cells from the media into the intima.[27,28] In this process, angiotensin II might act as a comitogen and stimulate increased proliferation of smooth muscle cells that have been activated to enter the cell cycle and have migrated to the subintima.[29] Based on the hypothesis that a local angiotensin system may regulate the vascular response to endothelial injury, Powell et al[30] examined the effects of various doses of the angiotensin converting enzyme (ACE) inhibitor cilazapril on neointimal proliferation in the rat carotid

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artery. Administration of a high dose resulted in an 80% reduction in neointima formation in this balloon-injured artery model.

The present multicenter, randomized, double-blind placebo-controlled trial was designed to test whether ACE inhibition can prevent late restenosis after PTCA in humans.

Methods

Study Population

All symptomatic and asymptomatic patients scheduled for PTCA with an angiographically proven, functionally significant narrowing in one or more major coronary arteries were considered for inclusion in 26 participating centers (see "Appendix"). A screening log was maintained in 17 participating centers. Between June 1989 and December 1989, 27% of patients screened in these centers were enrolled. Reasons for exclusion are listed in Table 1.

Treatment Allocation

The trial was carried out according to the Declaration of Helsinki (1963; revised in Venice, 1983). Informed consent was obtained in 735 recruited patients before the PTCA procedure. Patients were randomly assigned to cilazapril or placebo, but only 693 patients with successful PTCA (defined as a visually assessed diameter stenosis of <50% after PTCA) who met all inclusion and exclusion criteria as stated in the protocol continued the trial and formed the study population (Figure 1). Forty-two patients were excluded for the following reasons. 1) The PTCA procedure could not be performed (lesion not suitable). 2) The PTCA procedure was unsuccessful or unsatisfactory (either inability to reach or to cross the lesion or a diameter stenosis of >50% after PTCA, or abrupt occlusion not responding to intracoronary spasmolytic or thrombolytic therapy). 3) The PTCA procedure was complicated by myocardial

TABLE 1. Screening Results of 17 Log-Keeping Clinics

	n	%
Total number of screened patients	1,755	100
Number of recruited patients	478	27.2
Excluded from the trial	1,277	72.8
Reason for exclusion		
History of sustained essential hypertension	271	15.4
Previous and/or failed PTCA at the same site	268	15.3
Q wave MI <4 weeks before study entry	174	9.9
Follow-up coronary angiography unlikely	109	6.2
Logistic reasons	67	3.8
Significant concomitant disease	50	2.8
Older than 75 years	43	2.5
Dilatation of bypass graft	40	2.3
Primary perfusion therapy	39	2.2
No informed consent given	39	2.2
Current evidence or history of heart failure	28	1.6
Other reasons* (<1% each)	122	8.6

PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; MERCATOR, Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis; ACE, angiotensin converting enzyme.

*Participation in other trial; planned directional atherectomy procedure or stent implantation; left main disease; history of type II hypercholesterolemia; previous cerebrovascular accident; previous participation in MERCATOR; hypotension; contraindication to ACE inhibition/aspirin; women of childbearing potential; insulin-dependent diabetes; miscellaneous.

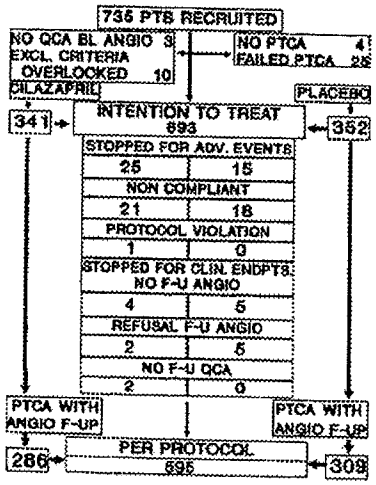

FIGURE 1. *Patient flowchart in MERCATOR (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis). Pts, patients; QCA, quantitative coronary angiography; BL, baseline; Excl, exclusion; PTCA, percutaneous transluminal coronary angioplasty; ADV, adverse; Clin endpts, clinical end points; F-UP, F-U, follow-up; ANGIO, angiogram.*

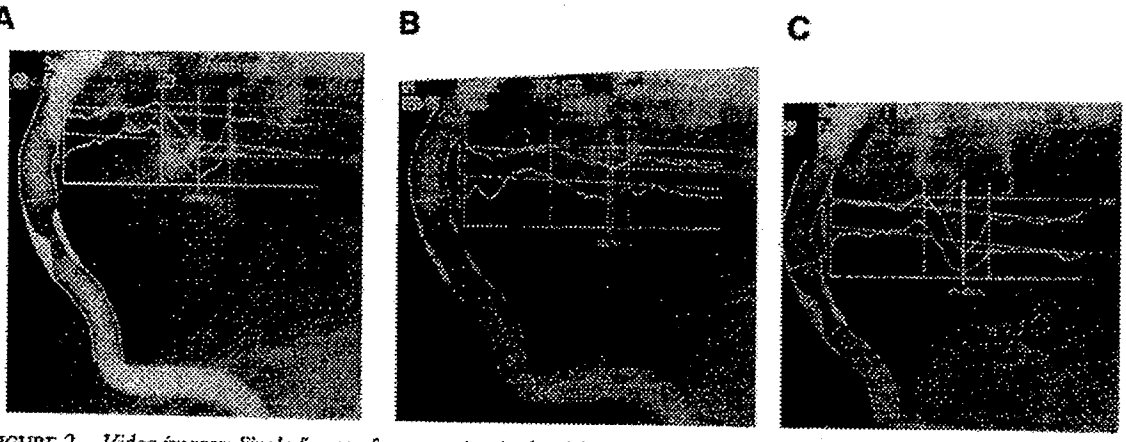

FIGURE 2. *Video images: Single frame of a narrowing in the right coronary artery before percutaneous transluminal coronary angioplasty (PTCA)* (panel A), *after PTCA* (panel B), *and at follow-up* (panel C). *Superimposed on the video image is the diameter function curve (upper curve) together with the interpolated reference curve. Minimal lumen diameter is 1.28 mm before PTCA, 2.58 mm after PTCA, and 1.17 mm at follow-up.*

infarction before the first drug intake (symptoms, ECG changes, and creatine kinase levels more than twice the upper limit of normal). Retroactively, patients were excluded from the study for the following reasons. 1) The baseline film could not be quantitatively analyzed. 2) The exclusion criterion was overlooked at the time of screening.

Trial medication was given for the first time in the evening after successful PTCA and consisted of either capsules of cilazapril (first evening, 2.5 mg; 5 mg b.i.d. thereafter) or matching placebo for 6 months. In addition, all patients received 75–125 mg aspirin b.i.d. before coronary PTCA until follow-up angiography.[31,32]

Follow-up Evaluation

Patients returned to the outpatient clinic after 1, 2, 4, and 6 months for an interview, a cardiac examination, ECG, laboratory tests, and a capsule count. Follow-up angiography was performed at the 6-month visit after the trial medication was discontinued. When symptoms recurred within 6 months, coronary angiography was carried out earlier. When no definite restenosis was present and the follow-up time was less than 3 months, the patient was asked to undergo another coronary angiogram at 6 months.

One to 4 days before follow-up angiography but after discontinuation of the trial medication, a symptom-limited exercise test was performed on a bicycle ergometer according to a standard protocol. The test was performed with the patient in a sitting position, starting with a work load of 20 W, which was increased by 20 W every minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or an ST depression of more than 1 mm occurred or the patient stopped because of fatigue. A 12-lead ECG was recorded during exercise and recovery. ST changes were measured 80 msec after the J point.

PTCA Procedure and Angiographic Analysis

At the beginning of the procedure, all patients received a bolus of 10,000 IU intravenous heparin. After 2 hours, an additional infusion of 5,000 IU/hr was given until the end of the procedure. Use of a calcium channel blocker for 48 hours after PTCA was permitted. Choice of balloon type, inflation duration, and pressure were left to the operator.

For the purpose of the study, three coronary angiograms were obtained in each patient—one just before PTCA, one immediately after PTCA, and one at follow-up. Angiograms were recorded in such a way that they were suitable for quantitative analysis by the Coronary Angiography Analysis System (CAAS). An example of an analysis is shown in Figure 2. To standardize the method of data acquisition and to ensure exact reproducibility of post-PTCA and follow-up angiograms, measures were taken as described earlier.[21,33] All angiographic analyses, including qualitative assessment of certain lesion characteristics,[34–36] were performed at a core laboratory, which was blinded to treatment allocation and did not have access to clinical data.

As visual assessment of coronary angiograms is hampered by a large interobserver and intraobserver variability,[33,37] all cineangiograms were quantitatively analyzed using the CAAS system, which has been validated and described in detail.[33,38] The absolute values of the stenosis diameter as well as the reference diameter are measured by the computer, using the known contrast–empty catheter diameter as a scaling device. To achieve maximal vasodilatation, intracoronary nitroglycerin or isosorbide dinitrate was given for each coronary artery involved before PTCA, after PTCA, and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for pincushion distortion introduced by the individual image intensifiers. Because the algorithm is not able to measure total occlusions and lesions with TIMI-1 perfusion, a value of 0 mm was used for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases, the post-PTCA reference diameter was used as the reference diameter before PTCA or at follow-up.

End Points

The primary end point of this study was the within-patient change in minimal lumen diameter as deter-

mined by quantitative angiography after PTCA and at follow-up. Post-PTCA values were obtained from the last post-PTCA angiogram made directly after removal of the guide wire. The initial procedure was considered finished when the guide catheter was removed. In the case that the clinical condition required repeat PTCA, the angiogram made before repeat PTCA was used to obtain follow-up values irrespective of the timing of repeat PTCA (hours, days, or weeks).

For each dilated segment, the minimal lumen diameter was taken as the mean value from multiple matched projections. Within-patient change was defined as the follow-up value minus the post-PTCA value. In the case that more than one segment was dilated (multivessel or multisite procedures), the mean change over all lesions dilated was taken as the end point. Secondary end points were restenosis rates, exercise test results, and clinical events. These were death (irrespective of cause), New York Heart Association class III–IV as a result of congestive heart failure, nonfatal myocardial infarction (symptoms, ECG changes, and creatine kinase enzymes above twice the upper limit of normal), coronary revascularization (CABG, repeat PTCA, stent implantation, or atherectomy at the same site or other site), and recurrent angina requiring initiation or increase in medical therapy, or none of the above. Only revascularizations that were done before the 6-month time window (6 months±3 weeks) were counted as a clinical event.

Statistical Methods and Analysis

As stated in the original protocol, the required sample size (200 evaluable patients per treatment group) was based on the assumption of a restenosis rate of 30% in the control group and of 15% (i.e., a 50% difference) in the cilazapril group (two-sided test with an α error of 0.05 and a power of 0.80). However, as more and more quantitative data became available, we realized that restenosis should be viewed as a continuous process. This is best measured by the mean overall change in absolute minimal luminal diameter instead of applying arbitrarily selected cutoff criteria of 50% diameter stenosis at follow-up or ≥0.72-mm change in minimal diameter between post-PTCA and follow-up. Consequently, the initial power calculations were changed during the trial in a protocol amendment with continuous data. With the assumption of a change of -0.40 ± 0.50 mm in mean minimal lumen diameter between postangioplasty and follow-up angiogram in the control group and -0.25 ± 0.50 mm (i.e., a 37.5% difference) in the active drug group (two-sided test with an α error of 0.05 and a power of 0.90), the minimal sample size was estimated to be 233 patients in each group. Thus, enough patients were recruited to detect a significant difference between the two treatment groups.

For statistical evaluation, intention-to-treat and per-protocol populations were defined. The intention-to-treat population comprised patients who fulfilled all inclusion and exclusion criteria and received at least one dose of test medication. The per-protocol population consisted of all compliant patients of the intention-to-treat population who had an analyzable follow-up angiogram. A patient was judged compliant if at least 80% of the test medication was taken and the test medication was not stopped more than 5 days before follow-up angiography.

To test the hypothesis that the mean change in minimal lumen diameter is equal in the two treatment groups, ANOVA was done with treatment and center as main factors and treatment times center as interaction term. As the change in minimal luminal diameter after PTCA follows a near-gaussian distribution, parametric tests were allowed to be used.[39] The treatment effect was defined as the difference in mean change in minimal lumen diameter between the two treatment groups. In addition, 95% confidence intervals of the treatment effect were obtained from the ANOVA.

Comparison of the clinical outcome was done for the intention-to-treat population. Each patient was assigned at the time of follow-up to the most serious applicable event on the scale described above. For comparison of the clinical outcome between the two treatment groups, standard nonparametric statistical methods were used.

Results

In total, 735 patients gave informed consent, and subsequently, 693 continued the trial and constituted the intention-to-treat population. Figure 1 shows the patient flowchart. Forty-two patients (23 patients randomly assigned to cilazapril and 19 patients to placebo) were not included in the trial for the following reasons. In four patients, no PTCA was performed because the lesion was no longer an indication for PTCA; in 25 patients, the outcome of the PTCA procedure was unsatisfactory (two patients with a post-PTCA diameter stenosis of >50% by visual assessment), unsuccessful (11 patients because of inability to cross the lesion), or complicated (four patients with emergency CABG, eight patients with sustained occlusion). Thirteen patients were excluded from the analysis (10 because a selection criterion was overlooked, three because no baseline quantitative analysis was possible). Of the remaining 693 patients, 352 were randomized to receive placebo and 341 were randomized to receive cilazapril.

Baseline Characteristics and Clinical Follow-up

Selected demographic and clinical characteristics of the two study groups are shown in Tables 2 and 3. In general, baseline characteristics were evenly distributed in the two groups except for patients with pain at rest and patients currently smoking, who were more frequently encountered in the control group.

Clinical follow-up was obtained for all 693 patients. During the course of the study, five patients died (control, two; cilazapril, three). The cause of death was cardiovascular in four cases and of other origin in one case. Nonfatal myocardial infarction was documented in 13 patients (control, eight; cilazapril, five); 17 patients underwent bypass surgery (control, eight; cilazapril, nine); repeat PTCA, atherectomy, or stent implantation was performed in 87 patients (control, 43; cilazapril, 44); and recurrent angina was observed in 135 patients (control, 67; cilazapril, 68). Finally, 224 (64%) in the control group and 212 (62%) in the treated group were event free at 6-month follow-up. Table 4 shows the number of events on a per-patient basis, with only the most serious event listed. Adjusted χ^2 test revealed no difference in ranking between the two groups.

During follow-up, 40 patients stopped their treatment because of adverse experiences (hypotension: control, one; cilazapril, nine; cough: control, none; cilazapril, four; rash: control, three; cilazapril, two; dizziness:

TABLE 2. Clinical Characteristics of the Intention-to-Treat Population

	Control patients (n=352)	Cilazapril patients (n=341)
Men (No.)	292 (83%)	282 (83%)
Age (years)	56±8 (32–74)	57±9 (35–74)
Ever smoked	269 (76%)	259 (76%)
Current smokers*	70 (20%)	49 (14%)
Non–insulin-dependent diabetes	20 (6%)	21 (6%)
One-vessel disease	228 (65%)	225 (66%)
Two-vessel disease	106 (30%)	99 (29%)
Three-vessel disease	18 (5%)	17 (5%)
Total cholesterol (mg/dl)	228±59	227±54
No angina present	30 (9%)	28 (8%)
Angina present	322 (91%)	313 (92%)
CCS class I	46 (13%)	53 (16%)
CCS class II	108 (31%)	103 (30%)
CCS class III	102 (29%)	100 (29%)
CCS class IV	66 (19%)	57 (17%)
Pain at rest*	133 (38%)	99 (29%)
Controlled by oral medication	92	64
Controlled by nitrates (i.v.)	28	15
Controlled by maximal medication	11	16
Continues at maximal medication	2	4
Duration of angina (days)	432±902	422±921
Previous MI	146 (41%)	142 (42%)
Previous CABG	6	7
Previous angioplasty	6	4
PTCA+CABG	1	1
No. of patients on		
Nitrates	246 (70%)	236 (69%)
Ca antagonists	228 (65%)	217 (64%)
β-Blockers	182 (52%)	180 (53%)
No medication	14 (4%)	19 (6%)
Monotherapy	89 (25%)	91 (27%)
Double therapy	180 (51%)	151 (44%)
Triple therapy	69 (20%)	80 (23%)

CCS, Canadian Cardiovascular Society angina classification; MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
Values are mean±SD. *$p<0.05$.

control, two; cilazapril, three; gastrointestinal problems: control, three; cilazapril, four; other reasons: control, five; cilazapril, four). Nine patients stopped treatment because they had a clinical event (death: control, two; cilazapril, three; CABG: control, one; cilazapril, one; nonfatal myocardial infarction: control, two; cilazapril, none), and one patient became a protocol violator. Thirty-nine patients did not fulfill compliance criteria (control, 18; cilazapril, 21); in nine patients, no angiogram suitable for quantitative analysis could be obtained due to either refusal (control, five; cilazapril, two) or to technical reasons (absence of matched views or poor quality of the follow-up film: control, none; cilazapril, two). Thus, the per-protocol population consisted of 309 control patients and 286 patients treated with cilazapril.

TABLE 3. Angiographic Characteristics of Per-Protocol Population

	Control patients (n=309, 367 lesions)	Cilazapril patients (n=286, 342 lesions)
Vessel dilated		
RCA	103 (28%)	101 (30%)
LAD	173 (47%)	153 (45%)
LCx	93 (25%)	88 (25%)
Number of sites dilated		
One	305 (82%)	283 (82%)
Two	51 (15%)	51 (15%)
Three	8 (2%)	7 (2%)
Four	3 (1%)	1 (1%)
Lesion type		
Concentric	188 (51%)	179 (52%)
Eccentric	135 (37%)	108 (31%)
Tandem	3 (1%)	18 (5%)
Multiple irregularities	31 (8%)	25 (7%)
Total occlusion	10 (3%)	12 (4%)
Calcified lesion	45 (12%)	46 (14%)
Side branch in stenosis	213 (58%)	197 (56%)
Lesion at bend point	34 (9%)	48 (13%)
Thrombus after PTCA	10 (3%)	14 (4%)
Dissection*		
No*	262 (72%)	235 (69%)
Type A	32 (9%)	39 (12%)
Type B	57 (16%)	49 (15%)
Type C	12 (3%)	13 (4%)
Type D	1	1
Type E	0	2
Largest size balloon (mm)	2.88±0.41	2.83±0.65
Maximal pressure (atm)	8.3±2.5	8.0±2.7
Total inflation (seconds)	245±226	247±214
Balloon artery ratio	1.14±0.20	1.12±0.18

RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; PTCA, percutaneous transluminal coronary angioplasty.
Values are mean±SD. *Modified from Reference 35.

Angiographic Efficacy Analysis

Table 5 summarizes the quantitative angiographic findings in the per-protocol population. On per-protocol basis, the loss at follow-up in minimal lumen diameter was −0.29±0.49 mm in the control group and

TABLE 4. Ranking per Patient Based on Most Serious Clinical Event During 6-Month Follow-up

	Control patients (n=352)	Cilazapril patients (n=341)
Death	2 (<1%)	3 (<1%)
NYHA III/IV	0	0
Nonfatal myocardial infarction	8 (2.3%)	5 (1.4%)
Coronary revascularization	51 (14.5)	53 (15.5)
Angina recurrence	67 (19.0%)	68 (19.9%)
No event	224 (63.6%)	212 (62.2%)

NYHA, New York Heart Association classification for congestive heart failure.

TABLE 5. Quantitative Analysis in the Per-Protocol Population

	Control patients (n=309)	Cilazapril patients (n=286)
Obstruction diameter (mm)		
Before angioplasty	0.98±0.35	1.05±0.35
After angioplasty	1.77±0.34	1.80±0.36
Follow-up	1.48±0.54	1.54±0.54
Reference diameter (mm)		
Before angioplasty	2.61±0.54	2.66±0.51
After angioplasty	2.67±0.48	2.72±0.49
Follow-up	2.68±0.56	2.74±0.52
Difference in obstruction diameter (mm)		
After preangioplasty	0.79±0.42	0.75±0.37
Follow-up postangioplasty	−0.29±0.49	−0.27±0.51
Percentage stenosis (%)		
Before angioplasty	61.4±13.4	60.1±12.3
After angioplasty	32.9±9.0	33.0±10.0
Follow-up	44.2±18.0	43.5±17.2
Difference in percentage stenosis (%)		
After preangioplasty	−28.5±15.3	−27.1±13.7
Follow-up postangioplasty	11.3±18.2	10.5±18.0

Values are mean±SD.

−0.27±0.51 mm in the cilazapril-treated group (treatment effect, 0.023 mm; 95% CI, −0.06–0.11 mm). Figures 3 and 4 represent a cumulative frequency curve of the minimal lumen diameter and of the change in minimal lumen diameter observed in both groups. Adjustment for current smoking and pain at rest did not affect the results. When participating clinics were analyzed separately, the results were consistent.

Table 6 summarizes the restenosis rates in the per-protocol population per lesion according to seven frequently used restenosis criteria.

Bicycle Ergometry

Of 693 patients, 564 (81%) underwent exercise testing at follow-up. Reasons for not performing the test were death in five patients (control, two; cilazapril, three), unstable angina in 58 patients (control, 30; cilazapril, 28), refusal in 18 patients (control, five; cilazapril, 13), adverse event in 23 patients (control, 11; cilazapril, 12), logistic reasons in six patients (control, four; cilazapril, two), and other reasons in 14 patients (control, five; cilazapril, nine). The exercise test was not performed according to protocol in five patients (control, four; cilazapril, one). Table 7 summarizes results of exercise testing in both groups. No difference in objective parameters was observed. Chest pain during exercise was reported in 74 patients (25%) receiving placebo and 42 patients (15%) receiving cilazapril (p=0.03). ST deviation (depression or elevation) of >0.1 mV associated with anginal symptoms was observed in 39 patients (13%) in the control group and 25 patients (9%) in the cilazapril group.

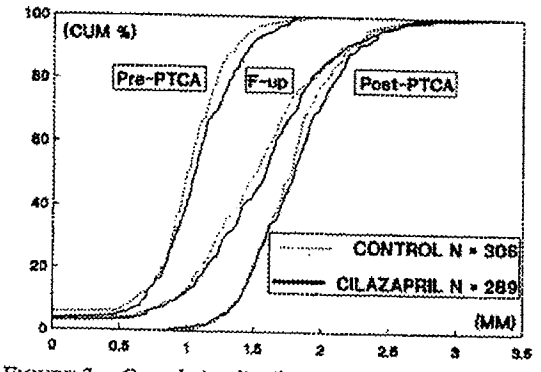

FIGURE 3. *Cumulative distribution curve (CUM %, cumulative percentage of patients) of the minimal lumen diameter before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at 6-month follow-up (F-up) in both treatment groups.*

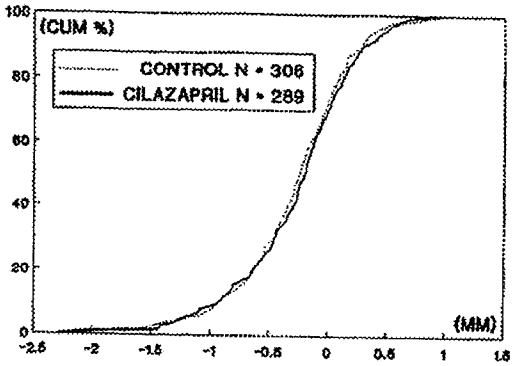

FIGURE 4. *Cumulative distribution curve of the change in minimal lumen diameter from before percutaneous transluminal coronary angioplasty (PTCA) to follow-up in both treatment groups. CUM %, cumulative percentage of patients.*

Discussion

Rationale for ACE Inhibition After PTCA

Over the past decade, it has been repeatedly demonstrated that treatment of chronic hypertensive rats with ACE inhibitors reduces the medial hypertrophy of muscular arteries.[40–42] Therefore, it has been postulated that the local renin–angiotensin system may participate in regulating the vascular response to arterial injury.

TABLE 6. Restenosis Rates per Lesion According to Frequently Used Definitions

	Control patients (n=309, 368 lesions)	Cilazapril patients (n=286, 342 lesions)
MLD (post-PTCA follow-up) ≥0.72	59 (16%)	56 (17%)
MLD (post-PTCA follow-up) ≥0.36	153 (42%)	129 (38%)
>30% DS increase in DS at follow-up	45 (12%)	42 (13%)
<50% DS after PTCA to >70% DS follow-up	25 (7%)	20 (6%)
DS follow-up <10% DS before PTCA	66 (18%)	55 (16%)
Loss of >50% of gain or >30% ↑ DS	144 (39%)	125 (37%)
<50% DS after PTCA to >50% DS follow-up	103 (28%)	96 (28%)

MLD, minimal lumen diameter; PTCA, percutaneous transluminal coronary angioplasty; DS, diameter stenosis.

TABLE 7. Exercise Test Results of 564 Patients

	Control patients (n=291)	Cilazapril patients (n=273)	p
Maximum work load (W)	146±39	151±44	NS
Exercise time (seconds)	446±124	454±127	NS
Systolic blood pressure at peak exercise (mm Hg)	196±27	192±28	NS
Heart rate at peak exercise (beats per minute)	142±22	142±21	NS
Double product (mm Hg · 100/beats per minute)	279±65	275±66	NS
ST deviation >1 mm	102 (36%)	99 (37%)	NS
Anginal symptoms during test	74 (25%)	42 (15%)	0.03
Combination of ST >1 mm and symptoms	39 (13%)	25 (9%)	NS

This hypothesis has prompted the investigation of the role of angiotensin II after injury. For this purpose, the effect of the long-acting ACE inhibitor cilazapril on the proliferative response to arterial injury was examined by Powell et al[30] in an animal model. This inhibitor was selected because at a dose of 10 mg/kg/day, it lowered blood pressure over a 24-hour period and reduced the medial hypertrophy of hypertensive rats. Using the same dose of cilazapril, neointima formation was decreased by 80% and lumen integrity was preserved in normotensive rats in which the left carotid artery was subjected to endothelial denudation and injury by balloon catheterization.[30]

More recently, several groups have studied the effects of angiotensin II on smooth muscle cell proliferation in vitro as well as the influence of ACE inhibition on smooth muscle cell proliferation. Angiotensin II induced expression of several growth factor genes, such as genes encoding PDGF, transforming growth factor-β (TGF-β), and thrombospondin (TS).[43–46] These results demonstrate that, in cultured cells, angiotensin II induces messenger ribonucleic acids to encode several important growth factor genes and thus induces cell proliferation. Cilazapril or its active metabolite did not have a direct effect by itself, but the antiproliferative effect was mediated through angiotensin II. Consequently, the inhibition of angiotensin II production may prevent the proliferative response that occurs after PTCA in humans.

Trial Design: Quantitative Angiography as Primary End Point

The primary goal of a restenosis prevention trial is the improvement in short-term and long-term clinical outcome of patients having undergone a PTCA procedure. It is assumed that the improvement in clinical outcome is related to an anatomical phenomenon, namely, the prevention of the recurrence of the stenosis in the treated vessel. However, in trials testing pharmacological compound with possible anti-ischemic or antianginal effects unrelated to the postinjury hyperplasia, the clinical outcome might be misleading and obscure the reason for the observed improvement. Quantification of luminal dimension changes over time may provide insight into the biological and mechanistic effects on the treatment after PTCA. The appearance (or reappearance) of angina as a sole criterion of restenosis underestimates the angiographic rate of restenosis. The poor value of recurrent anginal symptoms as a marker of restenosis is confirmed by the low predictive value of symptoms found in many studies.[18] Similarly, the usefulness of ergometry to detect restenosis after PTCA has been questioned since several studies have found that the presence of exercise test–induced angina or ST segment depression/elevation or both are not highly predictive for restenosis when the test is performed early or late after PTCA.[18] A drug tested for its ability to prevent restenosis may be shown to be beneficial after PTCA by reducing angina during exercise testing and yet have no effect on intimal hyperplasia after balloon-induced injury.

In the present study, fewer patients in the cilazapril-treated group experienced anginal pain during exercise testing. This symptomatic beneficial effect was not corroborated by an increase in work load or in double product or by ST changes. It must be emphasized that this difference in behavior between the two groups remains unexplained and had no bearing on the general outcome of the trial.

TABLE 8. Prognostic Value of Minimal Lumen Diameter at Follow-up in the Per-Protocol Population Divided Into Five Equal Groups

	Exercise test		Clinical outcome			
MLD follow-up (mm)	<1 mm ST changes and no chest pain	≥1 mm ST changes and chest pain	MI	Reintervention	Angina	None
<1.10	70 (75%)	24 (26%)	5 (4%)	49 (41%)	24 (20%)	41 (35%)
1.10–1.39	88 (88%)	12 (12%)	1 (1%)	18 (15%)	25 (21%)	74 (63%)
1.39–1.63	103 (90%)	11 (10%)	2 (2%)	10 (8%)	31 (26%)	77 (64%)
1.63–1.91	99 (93%)	8 (7%)	1 (1%)	7 (6%)	21 (15%)	89 (75%)
≥1.91	111 (98%)	2 (2%)	1 (1%)	7 (6%)	18 (15%)	94 (78%)
Total patients	471	57	10	91	119	375

MLD, minimal lumen diameter; MI, myocardial infarction.

In contradistinction, the prognostic value of the change in sequential coronary angiogram has been largely underestimated as a surrogate end point for clinical atherosclerotic events. In the second phase of the pharmacological investigation, the main emphasis should be put on the pathophysiological mechanism of prevention of restenosis in the postinjury model, and the improvement in clinical outcome should be viewed as a secondary benefit dependent on the anatomical status.

When the patient population of this trial is stratified according to the minimal lumen values at follow-up, it appears that the percentage of patients having reached one of the predefined clinical end points is as high as 65% in the worst category (minimal lumen diameter at follow-up <1.10 mm), whereas the percentage of event-free patients ranges from 63% to 78% in the other categories (Table 8). It must be emphasized that 41% of the patients in the worst anatomical category had reintervention versus only 6% in the best anatomical category irrespective of the initial dilatation site. Besides the prognostic value, the anatomical results also have a clear functional impact because only 2% of the patients had a positive exercise test in the best anatomical category versus 26% of the patients in the worst anatomical category.[47]

Lack of Effect on Angiographic Restenosis

The lack of angiographic effect in MERCATOR (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis) might have been dilution because of the loss to angiographic follow-up. If cilazapril had an important effect on restenosis, then clinical events such as sudden death, etc., would have predominated in the placebo group. Inasmuch as such events lead to loss to angiographic follow-up, angiographic restenosis might have been underestimated in the placebo group but not in the cilazapril group. Dilution would also occur if patients who are completely asymptomatic refuse repeat angiography. This kind of distortion (bias) of the effect assessment in an angiographic restenosis trial cannot be avoided as a matter of principle. Because there was no difference in clinical events leading to loss to angiographic follow-up and because the percentages of patients who had angiographic follow-up was relatively high (cilazapril, 94%; control, 94%), we do not believe that the lack of angiographic effect of cilazapril observed relates to loss to angiographic follow-up.

Several explanations (which are not mutually exclusive) may account for the apparent failure of cilazapril to decrease the rate of coronary restenosis.

Dose Relation

The dose selected for this trial was based on pharmacokinetic data in healthy volunteers, demonstrating that a single dose of 5 mg cilazapril reduced the plasma ACE activity to virtually unmeasurable levels.[46,49] Pharmacokinetic data from hypertensive patients demonstrate that after a single dose of 5 mg cilazapril, the plasma angiotensin II concentration starts to return to baseline in 8–10 hours, although a sustained blood pressure reduction is achieved. Therefore, the dosage of 5 mg b.i.d. was chosen.

After the trial was designed, it was shown that inhibition of neointima formation is a dose-dependent phenomenon and that the dose required for inhibition of neointimal formation appears to be somewhat higher than for lowering blood pressure.[46] In the rat model, this dose relation for the antiproliferative effect of cilazapril is different from the dose relation for the antihypertensive effect. Thus, a possible explanation for the lack of effect in MERCATOR is that the dose used was too low, as the dose used in the rat model was 70 times higher (10 mg/kg/day). The ongoing American/Canadian sister trial to MERCATOR, MARCATOR, which is similar in design but randomizes between 1, 5, and 10 mg of cilazapril b.i.d., will give us the unique opportunity to further investigate this relation in humans. If the antihypertensive effect in the 10 mg–b.i.d. subset of patients does not materially differ from that in the two other arms of the trial (1 and 5 mg b.i.d.), although a direct antiproliferative effect is observed, further investigation of the role of the renin–angiotensin system in tissue proliferation after vascular injury seems warranted.

Time Relation

As in animal experiments, no major difference in inhibition of neointimal proliferation was observed whether the drug was given 1 hour before or within 2 days after the wall injury. It was assumed that ACE inhibition by cilazapril could be started immediately after PTCA.[30]

In experimental studies, the strongest inhibition of neointima formation was obtained when treatment was started 6 days before injury. It could be that a period of drug impregnation before injury might be required to obtain an inhibitory effect, although a significant but slightly attenuated effect was observed when it was started 2 days after injury.

Species Relation

Powell et al[46] compared the effects of high doses of cilazapril (10 mg/kg/day) and captopril (100 mg/kg/day) on neointimal proliferation in the rat carotid artery model. Both agents were highly effective and, in addition, concomitant heparin therapy appeared to exert a synergistic antiproliferative effect. Similarly, in the atherosclerotic rabbit iliac model, cilazapril (5 mg/kg/day) reduced the incidence of restenosis after balloon injury.[50] In contrast, Lam et al[51] found no benefit of high-dose cilazapril (20 mg/kg b.i.d.) in the porcine carotid artery injury model. Churchill et al[52] and Huber et al[53] could not demonstrate significant benefit of captopril or enalapril in preventing restenosis in the swine model. Despite the fact that all species show an effect on blood pressure, the postinjury proliferation in baboons and pigs was not clearly affected by cilazapril at the doses used, whereas rats, guinea pigs, and rabbits did respond.[54] Rakugi et al[55] have shown that vascular injury results in the induction of ACE in proliferating cells in the neointima and supports the role of the local renin–angiotensin system in restenosis. Although quite attractive, the close parallel between the muscular response to experimental arterial injury and the development of restenosis in humans after therapeutic angioplasty remains a working hypothesis. The response of atherosclerotic human arteries may be modulated by cellular and molecular influences that are not exactly

similar to those acting in nondiseased nonhuman arteries.

Alternative Pathways of Angiotensin II Production

Other enzymes besides ACE are known for their ability to metabolize angiotensin I to angiotensin II (chymase, tonin, and cathepsin). It could well be that these alternative pathways resulted in sufficient levels of angiotensin II to activate or to stimulate the restenosis process. Because no actual measurement was done of angiotensin I or II, it is difficult to say whether these alternative pathways were active. However, we found a significant decrease in blood pressure immediately after the first drug intake in patients randomized to cilazapril compared with patients taking placebo. This effect was maintained during the entire 6-month follow-up period. Thus, clinically, there was an effect of cilazapril by reducing blood pressure, presumably by lowering the level of angiotensin II. The use of an angiotensin II receptor blocker might be worth exploring,[56] as in this case all angiotensin II, irrespective of the metabolic pathway that is used, is blocked.

Possible Mitogenic Effect of Angiotensin I

Another explanation for failure of cilazapril to reduce restenosis is that as a logical consequence of the use of ACE inhibitors, the concentration of angiotensin I is increased, which has been shown to be mitogenetic for arterial muscle cells.[45] This unavoidable side effect of ACE inhibitors may, perhaps only in some species, annihilate their favorable actions exerted through angiotensin II suppression.

Relevance of Mechanism of Action

The most recent theory on restenosis put forward by Lindner and Reidy[12] indicates that bFGF released after disruption and cell necrosis of the endothelium and media is the factor that initiates the proliferation and duplication of the smooth muscle cells. These subsequently activated smooth muscle cells tend to migrate in the subintima of the vessel, where they are attracted by the PDGF stemming from the aggregated platelets: It is in this location and stage that angiotensin II acts on them as a comitogen. This complex interaction may be the predominant biological scenario in certain species such as rat and rabbit but may be inoperative in other species such as the baboon and guinea pig.

Recently, Forrester et al[17] hypothesized that restenosis is a manifestation of the general wound-healing process expressed specifically in vascular tissue. They list five different groups of growth factors: PDGF, FGF, EGF (epidermal growth factor), IGF (insulin-like growth factor), and TGF (transforming growth factor), each with a specific role and with possibly many interactions. It is of course possible that angiotensin II has only a minor role in this complex process and that ACE inhibition did not result in less angiographic restenosis.

In contrast, Schwartz et al[57] hypothesize that mural thrombus is the most important factor in the restenosis process: It is seen in all treated animals after injury; after 3 days it is covered by endothelium, and later on, smooth muscle cells start to grow downward toward the media, suggesting that neointimal cells are probably not derived from arterial media at the immediate injury site.

Conclusions

Long-term ACE inhibition with cilazapril in a dose of 5 mg b.i.d. does not prevent restenosis and does not favorably influence the overall clinical outcome after PTCA in patients. The results of the MARCATOR trial must be awaited to see whether a higher dose of cilazapril has any effect on angiographic restenosis.

Appendix

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Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial

Thibaud Meurice, Christophe Bauters, Xavier Hermant, Valérie Codron, Eric VanBelle, Eugène P Mc Fadden, Jean-Marc Lablanche, Michel E Bertrand, Philippe Amouyel

Summary

Background The DD genotype for the angiotensin-I converting enzyme (ACE I) deletion allele (D) polymorphism is a possible genetic risk factor for restenosis after coronary stent implantation. We aimed to establish whether or not blockade of ACE with high doses of ACE inhibitors could reduce this risk of angiographic restenosis.

Methods We characterised the ACE I/D polymorphism in 345 consecutive patients who were undergoing coronary stenting. 115 had the DD genotype. We assigned 91 of these 115 patients to quinapril 40 mg daily (n=46) or placebo (n=45). Treatment was started within 48 h after stent implantation and continued for 6 months. 79 patients complied with the protocol and underwent follow-up angiography after 6 months.

Findings Our primary endpoint of late loss in minimum lumen diameter (a quantitative index of restenosis) was significantly higher in the quinapril group than in the controls (mean 1·11 mm [SD 0·70] *vs* 0·76 mm [0·60]; p=0·018). Secondary endpoints also showed consistent trends towards increased angiographic restenosis in the treatment group.

Interpretation Contrary to our expectations, ACE inhibitor treatment did not reduce restenosis after coronary stent implantation in patients with DD genotype, but was associated with an exaggerated restenotic process when compared with administration of placebo.

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Introduction

Coronary stent implantation reduces both angiographic restenosis and clinical events by comparison with balloon angioplasty in some patients.[1,2] However, the procedure leads to an iatrogenic condition, in-stent restenosis, that is more and more common and difficult to treat. Some factors predisposing to in-stent restenosis, such as the number of stents implanted or the size of the reference vessel, are procedure related. Some patients seem to have an inherent genetic susceptibility to in-stent restenosis though. We and others have shown that patients homozygous for the deletion (D) allele of the angiotensin-I converting enzyme (*ACE*) gene polymorphism, are at a raised risk of restenosis after stent implantation.[3,4] These individuals have raised concentrations of circulating and cellular ACE that could contribute to an accelerated growth response of smooth-muscle cells, leading to restenosis.[5] In this context, ACE inhibition could modify the consequences of these increased ACE concentrations in DD patients.

Results of a series of studies, which tested the hypothesis that ACE inhibitors—by virtue of their antiproliferative effects on smooth-muscle cells—might prevent restenosis after conventional balloon angioplasty, failed to show any effect on angiographic or clinical restenosis.[6,7] These negative findings are partly explained by other trial results, which suggest that restenosis after balloon angioplasty is mainly caused by vessel remodelling (a form of chronic vessel shrinkage) at the site of angioplasty, and that neointimal proliferation, previously thought to be the main mechanism of restenosis, plays only a minor part.[8]

The scaffolding effect of stent implantation eliminates remodelling, and in-stent restenosis has been conclusively shown by angiographic and intravascular ultrasound studies to be related to neointimal proliferation.[9] We designed a randomised, double-blind, placebo-controlled pharmacogenetic trial, to establish whether or not blockade of ACE with high doses of ACE inhibitors could limit neointimal proliferation and thus reduce angiographic restenosis after stent implantation in patients carrying the DD genotype.

Methods

Participants

546 patients who had an NIR stent (Boston Scientific, Natick, MA, USA) successfully implanted in our centre between January, 1998, and June, 1999, were eligible for inclusion immediately after the procedure. Our study protocol was approved by the ethics committee of the University Hospital, Lille, France, and written informed consent was obtained from all patients. We excluded patients who were aged 75 years or older, were women of childbearing potential, had had acute myocardial infarction within 48 h before stent implantation, had a systolic blood pressure of less than 120 mm Hg, needed ACE inhibitor or angiotensin II antagonist treatment, had renal or hepatic impairment, had a history of bleeding, had a contraindication to aspirin or ticlopidine, had had angioplasty of a saphenous-vein-graft lesion, or were participating in another study.

Study protocol

To keep to a minimum the time between coronary stenting and the first dose of ACE inhibitor, we developed a rapid genotyping technique. We established ACE genotype within 12–24 h of coronary stenting in all patients who gave informed consent for genotyping. Briefly, we added 60 µL of 0·5% lauryl sarcosyl in a red-cell lytic buffer (tris HCl 7·7 mmol/L, magnesium chloride, 6 H_2O 5 mmol/L, sodium chloride 10 mmol/L, pH 7·6) to 15 µL of whole blood in an EDTA tube. The sample was incubated for 40 min at 90°C and centrifuged (10 min, 5600 *g*). We used 5 µL of the supernatant to amplify and identify ACE genotype.[3] For all patients, the results were checked with classic DNA extraction techniques.[3] DD patients were randomly assigned to receive quinapril (40 mg daily for 6 months) or identical placebo tablets. Investigators and patients were unaware of treatment allocation, which we established before the start of the study. Trial medication was started within 48 h of coronary stent implantation. The first dose consisted of 20 mg of quinapril or matching placebo followed by 40 mg daily of quinapril or matching placebo for 6 months. Patients also received aspirin (75–300 mg daily) for 6 months and ticlopidine (500 mg daily) for 1 month.

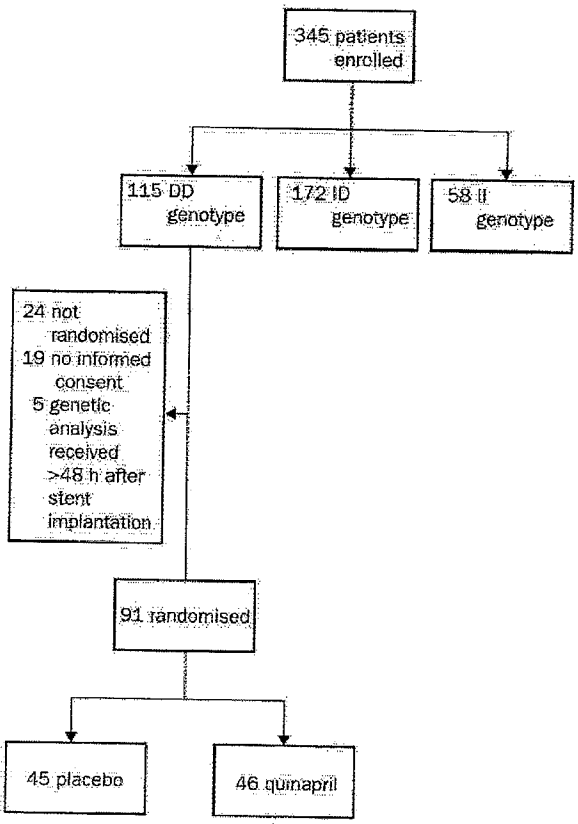
Patients returned to the outpatient clinic after 3 and 6 months for interview, physical examination, tablet count, and electrocardiography. We did telephone interviews at 1, 2, and 5 months to record clinical events and use of trial and concomitant medications. Follow-up angiography was done at the 6-month visit after trial medication was discontinued. If symptoms recurred within 6 months, coronary angiography was done earlier than planned. When follow-up angiography was done less than 3 months after the procedure, and did not suggest restenosis, we asked the patient to undergo another follow-up coronary angiogram at 6 months.

At the beginning of the coronary stent implantation procedure, all patients received a bolus of 70 IU/kg intravenous heparin. We judged the procedure as having been a success if the residual stenosis was visually estimated as being less than 20%, without major complication. We did quantitative computer-assisted angiographic measurements in matched projections with use of the Cardiovascular Measurement System (Medical Imaging System, Leiden, Netherlands).[10] Patients received intracoronary isosorbide dinitrate to achieve maximum vasodilation. We used the following definitions: acute gain associated with the procedure was defined as the difference between minimum lumen diameter (MLD) immediately after stent implantation and MLD before the procedure; late loss during follow-up was the difference between MLD immediately after stent implantation and MLD at follow-up; and loss index was the ratio of late loss to acute gain.

Our primary endpoint was change in MLD during follow-up (late loss) determined by quantitative angiography on angiograms done immediately after coronary stenting and at 6-month follow-up. Secondary endpoints were loss index, MLD at 6 months, percentage of diameter stenosis at 6 months, and binary-angiographic-restenosis rate, defined as 50% or more at the stented site at follow-up.

Statistical analysis

In a previous study[3] workers recorded a mean late loss of 0·89 mm (SD 0·61) 6 months after coronary-stent implantation in patients with the DD genotype. We calculated that 72 patients were needed to detect a 40% reduction in late loss by quinapril during the 6 months after coronary stenting, with a statistical power of 0·80 and a one



Trial profile

tailed significance value of 0·05. Assuming a drop out rate of 10%, and a 90% rate of compliance with the protocol, we increased the target sample size by about 20 patients, to 90.

Statistical analysis was done with SAS software (version 6.12). A two-tailed p value of <0·05 was judged significant. Qualitative variables were compared between the two groups with use of χ^2 test or Fisher exact test. Quantitative variables were compared between groups with ANOVA and Wilcoxon non-parametric test. Quantitative data are presented as mean (SD), and qualitative data as number (%).

The intention-to-treat population included all patients who took at least one dose of study medication. For the angiographic analysis in the intention-to-treat population, patients who refused follow-up angiography were allocated an MLD of zero at follow-up—this value being regarded as the worst case value according to our original analysis plan. The per-protocol population was defined as patients with a confirmed DD genotype who were more than 80% compliant with treatment and underwent angiographic follow-up at 6 months.

Results

345 patients who fulfilled the inclusion criteria gave informed consent for ACE genotyping. The figure shows genotyping results and the trial profile. The genotype distribution was in Hardy-Weinberg equilibrium. 115 (34%) patients had the DD genotype, 91 (79%) of whom were assigned to quinapril or placebo. Apart from hypertension and hypercholesterolaemia, which were more frequent in the controls than in the treatment group (p=0·03), baseline characteristics were similarly distributed in both groups (table 1).

Characteristic	Quinapril (n=46)	Placebo (n=45)
Characteristics of patients		
Mean age (SD) (years)	59·3 (10·5)	59·4 (10·7)
Sex: male	42 (91%)	36 (80%)
Smoking	39 (85%)	34 (75%)
Hypercholesterolaemia	31 (67%)	39 (87%)
Hypertension	17 (37%)	27 (60%)
Diabetes	9 (20%)	5 (11%)
Family history of coronary artery disease	29 (63%)	23 (51%)
Previous myocardial infarction	26 (57%)	18 (40%)
Unstable angina	9 (20%)	15 (33%)
Mean ejection fraction (SD)	53% (9%)	55% (11%)
Mean interval from stent implantation to follow-up (SD) (months)*	5·95 (0·59)	5·92 (0·63)
Stented vessel		
Left anterior descending artery	20 (44%)	20 (44%)
Circumflex	6 (13%)	7 (16%)
Right coronary artery	20 (44%)	18 (40%)
Lesion length (mm)		
<10	29 (63%)	20 (44%)
10–20	11 (24%)	17 (38%)
>20	6 (13%)	8 (18%)
TIMI grade		
0	2 (4%)	2 (4%)
1	1 (2%)	0
2	2 (4%)	2 (4%)
3	41 (90%)	41 (92%)
ACC/AHA classification		
A	6 (13%)	5 (11%)
B1	14 (30%)	9 (20%)
B2	19 (41%)	22 (49%)
C	7 (15%)	9 (20%)
Number of stents		
1	37 (80%)	39 (87%)
2	9 (20%)	6 (13%)
Mean stent length (SD) (mm)	17·87 (7·04)	18·98 (7·09)
Mean maximum balloon size (SD) (mm)	3·22 (0·43)	3·08 (0·45)
Mean maximum inflation pressure (SD) (atm)	14·7 (2·8)	14·1 (3·3)

TIMI=thrombolysis in myocardial infarction; ACC=American College of Cardiology; AHA=American Heart Association.
*n=87.

Table 1: **Baseline characteristics (intention to treat population)**

All 91 patients were followed up. No patients died; non-fatal myocardial infarction occurred in one individual assigned to quinapril. Three patients underwent coronary-artery-bypass surgery (all on quinapril); ten patients on quinapril and seven controls needed repeat angioplasty or stent implantation. 11 (24%) and seven (16%) patients taking quinapril and placebo, respectively, had at least one clinical event at 6 months. Of the 91 patients, two in the quinapril and one in the placebo group had the ID genotype when tested with standard techniques; six and three, respectively, did not fulfil compliance criteria; and three patients on quinapril and one control refused follow-up angiography. The final per-protocol population consisted of 38 patients on quinapril and 41 on placebo. In the quinapril group, 36 (95%) patients received the full 40 mg dose and two (5%) received a 20 mg dose.

Table 2 summarises the quantitative angiographic findings in our per-protocol population. The reference diameters before and after stent implantation and at 6-month follow-up were much the same in both groups. Late loss in MLD was higher in the quinapril group than in controls. Although not significant, differences in MLD at follow-up, percentage diameter stenosis at follow-up, and restenosis rate also showed a consistent trend towards increased restenosis in the quinapril group. In the intention-to-treat population, consistent results were obtained: late loss in MLD was mean 0·79 (SD 0·65) in the controls and 1·21 (0·93) in those on quinapril (p=0·015).

	Quinapril (n=38)	Placebo (n=41)	p
Reference diameter (mm)			
Before stent	3·03 (0·35)	3·01 (0·57)	0·840
After stent	3·18 (0·39)	3·14 (0·49)	0·663
Follow-up	3·08 (0·89)	3·02 (0·48)	0·568
Minimal lumen diameter (mm)			
Before stent	0·94 (0·43)	0·85 (0·39)	0·315
After stent	2·93 (0·46)	2·81 (0·50)	0·276
Follow-up	1·82 (0·76)	2·06 (0·79)	0·184
Stenosis (%)			
Before stent	69 (14)	72 (13)	0·347
After stent	8 (7)	10 (6)	0·098
Follow-up	41 (23)	33 (21)	0·091
Acute gain (mm)	2·09 (0·64)	1·96 (0·52)	0·856
Late loss (mm)	1·11 (0·70)	0·76 (0·60)	0·018
Loss index	0·60 (0·42)	0·40 (0·32)	0·018
Restenosis rate (>50%)	14 (37%)	10 (24%)	0·229

Figures are mean (SD).

Table 2: **Quantitative coronary angiography (per protocol population)**

Discussion

Contrary to our expectations, administration of an ACE inhibitor after coronary stenting in patients with the DD genotype did not reduce late loss in lumen diameter, but was in fact associated with an exaggerated restenotic process by comparison with placebo. All secondary angiographic indices also showed a consistent trend towards an increased restenotic process in the quinapril group (table 2). Furthermore, although the study was not powered to assess clinical outcome, there was a disturbing trend for an increase in major clinical adverse advents in the quinapril group compared with the control group.

We screened patients who underwent stent implantation as an adjunct to percutaneous intervention for coronary disease on the basis of their genotype for the ACE I/D polymorphism. To rapidly identify DD patients and assign them quickly during the planned hospital stay, we developed a new genotyping method. When compared with conventional methods, our rapid test of detection for DD carriers had a 100% sensitivity, a 98·7% specificity, and in our population a 97·4% positive predictive value and a 100% negative predictive value. This rapid detection approach has potential widespread applications in clinical practice.

Why can no clear explanation be advanced for our unexpected findings? Although this was a single-centre study, the baseline characteristics of the study population seem representative of patients undergoing coronary stent implantation in routine clinical practice. Moreover, the comparison of baseline characteristics between the groups does not provide a plausible explanation for the increased late loss in the quinapril group: hypercholesterolaemia and hypertension were significantly more frequent in the controls, but these factors have not been consistently linked with the occurrence of in-stent restenosis. Additionally, non-significant differences between groups were also noted in other confounding variables but were well balanced in terms of their potential to affect risk of restenosis. Although previous myocardial infarction and diabetes were more frequent in the quinapril group, unstable angina and long lesions were more common in the placebo group.

This trial provided a way to verify our primary biological hypothesis that was susceptible to underlie the association between the ACE D allele and restenosis. The renin-angiotensin system has been implicated in the pathogenesis of neointimal hyperplasia after vascular injury. Administration of ACE inhibitors inhibits neointimal

development after experimental balloon angioplasty:[11] this effect could be related to the role of ACE in the formation of angiotensin II[12] and in the degradation of bradykinin,[13] which are smooth muscle cell growth factors and inhibitors, respectively. Two studies looking for a relation between the ACE I/D polymorphism and restenosis after coronary stenting suggest a role for the renin-angiotensin system in the pathogenesis of restenosis.[3,4] Despite a recent negative publication,[14] the results of these studies suggest that the DD genotype could be a genetic risk factor for restenosis after coronary stenting. Our unexpected findings suggest that the primary biological hypothesis relating increased restenosis directly to raised concentrations of ACE in DD patients could be too simplistic. ACE inhibitors inhibit neointimal hyperplasia after experimental arterial injury; however, the pathogenesis of human restenosis after coronary stenting might differ substantially from what is seen in very simple animal models. For example, inflammation associated with coronary stent implantation has been suggested as a possible determinant of subsequent restenosis.[15] If this is the case, the higher bradykinin concentrations associated with ACE inhibition could increase the risk of restenosis via a proinflammatory effect.[16] This effect might be especially striking in DD patients with constitutionally high concentrations of ACE.

Our study raises questions for the use of ACE inhibitors in the months after coronary stenting. There was a disturbing trend towards an increase in major adverse cardiac events in those on quinapril. However, we emphasise that ours was an angiographic study that was not powered to analyse clinical endpoints. In the QUIET study,[17] quinapril treatment started after balloon angioplasty did not affect clinical outcome (Milton Pressler, personal communication). Additionally, these findings were observed in a highly selected study population (DD patients) and cannot be extrapolated to all patients undergoing coronary stenting. The effect of ACE inhibitors could differ according to the ACE genotype. In the BANFF study,[18] quinapril improved flow-mediated vasodilation in II and ID patients but not in DD patients. A larger study, adequately powered for clinical and angiographic endpoints, would thus be needed before any definitive recommendation on the use of ACE inhibitors after coronary stenting could be made, especially in view of the well documented benefit of this class of drugs in patients with coronary artery disease.[19] The effect of ACE inhibition should be studied in DD patients, but also in ID and II patients, to look for interactions between ACE inhibitor treatment and ACE I/D polymorphism. The potential benefit of pretreatment with an ACE inhibitor before coronary stenting should also be tested. Finally, we could analyse the effect of angiotensin II receptor antagonists, which might prevent stimulation of smooth muscle cells by angiotensin II without affecting bradykinin metabolism.

ACE inhibitors are widely prescribed in patients with atherosclerosis, hypertension, or diabetes, and after myocardial infarction, because of proven beneficial effects in each of these subgroups. However, these patient groups are the major referral base for stent implantation, a procedure done in more than a million individuals worldwide every year. Thus, with the results of our pharmacogenetical trial, showing a deleterious effect on angiographic restenosis of ACE prescription in DD carriers, with a consistent trend in all secondary angiographic and clinical endpoints, the medical community should be made aware of these albeit unexpected findings. Our results are not destined to change clinical practice but rather to draw attention to a potential difficulty.

Contributors

T Meurice and E VanBelle participated in the clinical organisation, patient follow-up, and angiographic measurements; J M Lablanche and M E Bertrand participated in the conception of the trial, clinical organisation, and quantitative angiography; X Hermant and V Codron participated in genetic analyses and in validation of analyses; C Banters and P Amouyel participated in the conception and design of the trial, in analysis and interpretation of data, and in writing of the report; E P Mc Fadden revised the report.

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